

REMARKS

In the Office Action under reply, the Examiner has rejected the claims as follows:

1. Under 35 U.S.C. §102(b) as anticipated by WO 97/16452 (claims 48-50, 53, 56, 57, 61, 68, 70-73, and 76-79);
2. Under 35 U.S.C. §102(b) as anticipated by Norman (claims 48-50, 53, 56, 57, 61, 68, 70-73, 77, and 79);
3. Under 35 U.S.C. §102(b) as anticipated by De Azevedo (claims 48-50, 53, 56, 57, 61, 68-73, and 76);
4. Under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 6,316,456 to Meijer et al. (claims 48-50, 53, 56, 57, 61, 68, 70-73, and 76);
5. Under 35 U.S.C. §102(b) as anticipated by Jacobsen (claims 48-50);
6. Under 35 U.S.C. §103(a) as obvious over Vesely (claims 48-50, 56, 57, 61, 68, 70-73, 77, and 79);
7. Under 35. U.S.C. §112, second paragraph, as indefinite (claims 48-50, 53-57, 59-62, 65-68, 70-73, and 76-78);
8. Under 35. U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (claims 48-50, 53-57, 59-62, 65-68, 70-73, and 76-78);
9. Under 35. U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention (claims 68 and 70-73); and
10. Under the judicially created doctrine of obviousness-type double patenting over claims 1-6 of U.S. Patent No. 5,866,702 and claims 92 et al. of copending U. S. Patent Application No. 09/929,771 (claims 1, 2, 8, 10, 14-16, 18, 20, 44-50, 53-62, and 65-67).

With the above amendments, claims 49, 53, 58, 68, 70-73, and 79 have been cancelled and claims 48, 50, 54, 59, and 65 have been amended. Thus, claims 48, 50, 54-57, 59-62, 65-67, and 76-78 remain pending in the application.

The Examiner's rejections and objections are addressed, in part, by the above-amendments and are otherwise traversed by the arguments presented below.

THE AMENDMENTS TO THE CLAIMS

Claim 48 has been amended to clarify the invention. The proviso language has been simplified so that it is clear that R₁' is not cyclohexylmethyl, phenyl, substituted phenyl, benzyl, phenylethyl, or m-hydroxybenzyl and that R₄ and R₅ are not both hydrogen. Support for this amendment can be found in the original provisos and in the detail recitation of substituents presented in the tables wherein cyclohexylmethylamino and anilino R₁ substituents are disclosed. See page 21, Table 1, entries 1 to 16, etc., page 30, Table 1, entries 1 and 5, etc.

Claim 48 has also been amended to specify that X is -NH- and to require that the possible R₄ and R₅ alkyl substituents be substituted. These amendments effectively incorporate the elements of dependent claims 49 and 53, which have accordingly been cancelled. The dependency of claims 50, 54, and 59 have been correspondingly amended.

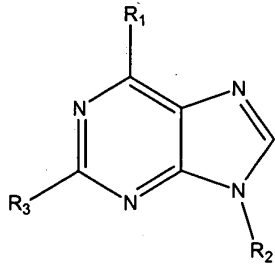
Claim 65 has been amended to remove redundant language regarding the R₃ substituent.

Claims 58, 68, 70 to 73, and 79 have been cancelled. Cancellation of these claims is without prejudice, without intent to abandon in any previously claimed subject matter, and without intent to acquiesce in any rejection of record.

No new matter has been added to the application by way of these specification and claim amendments.

THE CLAIM FOR PRIORITY:

The Examiner has maintained his refusal to accord the presently pending claims the August 2, 1996, priority date of the grandparent application, now issued U.S. Patent No. 5,866,702. Applicants continue to disagree with the Examiner regarding the existence of support for the claims in the grandparent application. The chart presented below clearly indicates the location of supporting disclosure for independent claim 48 in the issued grandparent application.

INDEPENDENT CLAIM 48	LOCATION OF SUPPORT IN U.S. PATENT No. 5,866,702
<p>A compound having the formula:</p>  <p>wherein:</p>	See the Abstract and remainder of patent.
<p>R₁ is -X-R₁'; in which R₁' is lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, or heterocycle, and X is -NH-;</p>	See column 2, lines 16 to 21.
<p>R₂ is lower alkyl optionally substituted with one, two or three groups chosen from hydroxy, lower alkoxy, and halogen; and</p>	See column 2, lines 23 to 27.
<p>R₃ is -NR₄R₅; in which R₄ and R₅ independently are hydrogen or lower alkyl optionally substituted with one, two or three groups chosen from hydroxy and amino,</p>	See column 2, lines 28 to 31.

INDEPENDENT CLAIM 48	LOCATION OF SUPPORT IN U.S. PATENT No. 5,866,702
<p>with the proviso that</p> <p>i. R₁' is not cyclohexylmethyl, phenyl, substituted phenyl, benzyl, phenylethyl, or m-hydroxybenzyl, and</p>	<p>Cyclohexymethyl substituents are disclosed in Table 1, column 9, next to last entry.</p> <p>Phenyl and substituted phenyl substituents are disclosed in Table 2 as anilino and substituted anilino substituents. See entries 4-6 in columns 15 and 16.</p> <p>Benzyl and m-hydroxybenzyl substituents are specifically recited in the provisos found in column 2, lines 55-64.</p> <p>Phenylethyl substituents are disclosed in column 9, Table 1, middle of column.</p>
<p>ii. R₄ and R₅ are not both hydrogen:</p>	<p>The possibility of R₄ and R₅ as hydrogen is clearly presented in the original claim language.</p>
<p>or an acid addition salt or cationic salt thereof</p>	<p>Acid addition salts and cationic salts are disclosed in column 6, lines 38 to 53.</p>

With respect to the added proviso language, applicants refer the Examiner to section 2173.05(i) of the MPEP. As stated in the third paragraph of this section, "[i]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." Given that cyclohexylmethyl, phenyl, substituted phenyl, benzyl, phenylethyl, and m-hydroxybenzyl were all disclosed in the parent application as R₁' substituents and that the possibility of R₄ and R₅ as hydrogen is clearly presented in the original claim language, proviso language excluding the specific R₁' substituents and prohibiting the specific combination wherein R₄ and R₅ are both hydrogen does not constitute new matter.

Based on the clear support for the presently pending claims in the grandparent application, independent claim 48 and all claims dependent thereupon are properly entitled to the benefit of the August 2, 1996, priority date.

THE REJECTION UNDER 35 U.S.C. §102(B) OVER WO 97/16452:

The Examiner has rejected claims 48-50, 53, 56, 57, 61, 68, 70-73, and 76-79 under 35 U.S.C. §102(b) as anticipated by WO 97/16452 and has specifically cited the compounds depicted by Figure 1 in the reference. As claims 49, 53, 68, 70-73, and 79 have been cancelled, the rejection, as it pertains to them, is now moot.

As amended herein, independent claim 48 excludes all compounds wherein R₁' is phenyl or substituted phenyl. Since the figure 1 compounds of WO 97/16452 all require a phenyl or substituted phenyl moiety at this position, they do not fall within the scope of the presently pending claims and, therefore, cannot anticipate the subject matter encompassed therein.

Given the reference's failure to disclose compounds having each and every element as set forth in the claims, applicants submit that reconsideration of the rejection is in order and request that the rejection be withdrawn.

THE REJECTION UNDER 35 U.S.C. §102(B) OVER NORMAN:

Claims 48-50, 53, 56, 57, 61, 68, 70-73, 77, and 79 have been rejected over Norman. As claims 49, 53, 68, 70-73, and 79 have been cancelled, the rejection, as it pertains to them, is now moot. As discussed above, the presently pending claims are entitled to the August 2, 1996, priority date of the grandparent application, now U.S. Patent No. 5,866,702. Norman, as discussed in the previous response, was not available to the public until August 7, 1996, as confirmed with The Journal of the American Chemical Society. Given this fact, Norman is not properly cited as 102(b) prior art and

the rejection is in error. Reconsideration and withdrawal of the rejection are in order and are earnestly requested.

THE REJECTION UNDER 35 U.S.C. §102(B) OVER DE AZEVEDO:

The Examiner has cited the disclosure in De Azevedo of roscovitine in his rejection of claims 48-50, 53, 56, 57, 61, 68-73, and 76. As claims 49, 53, 68, and 70-73 have been cancelled, the rejection, as it pertains to them, is now moot. Amended independent claim 48 excludes the possibility of benzyl substituents in the R₁' position. Given that roscovitine requires such a moiety, the disclosure by De Azevedo cannot be deemed anticipatory. Reconsideration and withdrawal of the rejection are in order and are hereby requested.

THE REJECTION UNDER 35 U.S.C. §102(B) OVER MEIJER ET AL.:

The Examiner has rejected claims 48-50, 53, 56, 57, 61, 68-73, and 76 over species 1-6, 10, 14-16 as disclosed in Table 1 of the patent. As claims 49, 53, 68, and 70-73 have been cancelled, the rejection, as it pertains to them, is now moot. Applicants disagree as all of the cited compounds are outside the scope of the presently pending claims.

Of the 18 compounds disclosed in Table 1, compounds 1-4, 8-16 and 18 contain an unsubstituted benzyl group in the R₁' position. As discussed above, this moiety is not allowed at this position in the pending claims. Compound 5 contains an isopentyl group as the -X-R₁' moiety, given that X must be -NH-, compound 5 also does not anticipate the pending claims. Compound 6 contains a cyclohexylmethyl group in the R₁' position, this is also an excluded substituent. Similarly, as compound 7 contains a chloro group in the R₃ position, compound 7 fails to anticipate. The remaining compound, compound 17,

contains a methanol pyrrolidine substituent in the R₃ position, which also falls outside the scope of the pending claims.

Applicants accordingly request reconsideration and withdrawal of the rejection over Meijer et al.

THE REJECTION UNDER 35 U.S.C. §102(B) OVER JACOBSEN:

The Examiner has rejected claims 48-50 over the iodoenzyl species 15 and 17-20 disclosed by the reference. As claim 49 has been cancelled, the rejection, as it pertains to that claims, is now moot. Applicants disagree with the rejection as all of the cited compounds are outside the scope of the presently pending claims.

Compound 15 contains an amino group as the R₃ substituent, i.e., both R₄ and R₅ are hydrogen. This combination is specifically excluded from the scope of the pending claims.

Compound 17-20 all contain unsubstituted alkyl groups in the R₄/R₅ position. These substituents are also not within the scope of the currently pending claims.

Reconsideration and withdrawal of the rejection is in order and is requested.

THE REJECTION UNDER 35 U.S.C. §103(A) AS OBVIOUS IN VIEW OF VESELY:

Claims 48-50, 56, 57, 61, 68, 70-73, 77, and 78 have been rejected as unpatentable over Vesely. As claims 49, 68 and 70-73 have been cancelled, the rejection, as it pertains to them, is now moot. The Examiner, while acknowledging that the compounds in Vesely do not anticipate the presently claimed invention, asserts that the presently claimed compounds are homologues of the compounds disclosed in Vesely and,

therefore, the close structural similarity is sufficient to show obviousness. Applicants disagree.

The Examiner has relied upon section 2144.09 of the MPEP wherein the patentability of compounds having a close structural similarity to known compounds is discussed. The Examiner argues that while olomoucine is not within the scope of the pending claims, modification of the compound to include an additional methyl group on the benzyl ring would create a methylated benzylamino substituted purine, a compound that is within the scope of the pending claims. Applicants submit that the Examiner is incorrectly applying the guidance provided by the MPEP.

As stated in section 2144.09,

The presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (appellant produced sufficient evidence to establish a substantial degree of unpredictability in the pertinent art area, and thereby rebutted the presumption that structurally similar compounds have similar properties); *In re Schechter*, 205 F.2d 185, 98 USPQ 144 (CCPA 1953).

In this instance, it is well accepted that any substitution, even of an exceedingly minor nature, may significantly impact the activity of a CDK2 inhibitor. Applicants direct the Examiner's attention to the profound variation in activity of the compounds presented in Table 2 of the Vesely reference itself. As the Examiner will see, the addition of a single methyl group, e.g., 6-dimethylaminopurine vs 6-trimethylaminopurine (compounds 2 and 3 in Table 1), will decrease the activity of the compound from that having a IC_{50} of 120 μ m to that having an IC_{50} of greater than 500 μ m.

While Vesely does disclose a number of possible substituents in the R_1' position, the compounds described in the reference do not suggest the compounds of the claimed invention. At best the teaching of Vesely could be seen as suggesting that further testing be done, but in no way can the results presented in the reference be seen as sufficient to create a reasonable expectation that further substitution would inevitably result in

retention of the compound's CDK2-inhibitory properties. The steric and electrochemical parameters and requirements of CDK2 binding are simply too complex for such broad assumptions to be made. Thus, while there might be a motivation to modify the compounds disclosed in Vesely, there would be no reasonable expectation that the proposed modification would successfully produce a CDK2 inhibitory compound. *Prima facie* obviousness does not exist.

The Examiner's presumption of obviousness is in error given the level of unpredictability in the art. Applicants earnestly and respectfully request that the Examiner reconsider and withdraw the rejection.

THE REJECTIONS UNDER 35. U.S.C. §112, SECOND PARAGRAPH, AS INDEFINITE:

The Examiner has rejected claims 48-50, 53-57, 59-62, 65-68, 70-73, and 76-78 as indefinite for a variety of reasons. As claims

1. Claim 71-"Cell Proliferative Disorders"

The Examiner's first enumerated rejection is based on his assertion that the term "cell proliferative disorder" fails to include a number of conditions specifically recited in claim 71. As claims 68 and 70-73 have been cancelled, this aspect of the 35. U.S.C. §112, second paragraph rejection is now moot. Applicants wish to formally state that the cancellation of these claims was done solely for the purpose of expediting prosecution of the composition claims and applicants expressly reserve the right and fully intend to prosecute the cancelled method claims in a later continuing application.

2-5. The Various Provisos (Presumably in Claim 48):

As the provisos have been rewritten in claim 48, these aspects of the 112 rejection are now moot.

6. The Determination of "in need thereof" in Claim 68:

As claims 68 and 70-73 have been cancelled, this aspect of the 35. U.S.C. §112, second paragraph rejection is also moot. Applicants stress once again that the cancellation of these claims was done solely for the purpose of expediting prosecution of the composition claims and applicants intend to prosecute the cancelled method claims in a later continuing application.

THE WRITTEN DESCRIPTION REJECTION UNDER 35. U.S.C. §112, FIRST PARAGRAPH:

Although the Examiner has stated that claims 48-50, 53-57, 59-62, 65-68, 70-73, and 76-78 have been rejected over 35. U.S.C. §112, first paragraph, as lacking written description in the specification, the Examiner's comments are only directed to claims 58 and 79. Applicants assume that the rejection was intended to cover only these two claims and will respond accordingly. Should the Examiner have intended to reject all of the claims indicated in the Office Action, applicants request that further clarification be provided as to the basis for the rejection of the additional claims.

The Examiner has based the rejection of claims 58 and 79 on a purported lack of description in the specification for the Markush group recited in the claims. The Examiner reasons that as the compounds covered by claims 58 and 79 were not specifically recited in a discrete subgrouping, a claim to these compounds is unsupported. Applicants disagree but in the interest of expediting prosecution, claims 58 and 79 have been cancelled. Applicants point out that the cancellation of these claims does not result in the abandonment of any previously claimed subject matter as the compounds encompassed by claims 59 and 79 also fall within the scope of the other pending claims.

Given that the presumably rejected claims have been cancelled, the rejection is now moot and its reconsideration and withdrawal are requested.

THE ENABLEMENT REJECTION UNDER 35. U.S.C. §112, FIRST PARAGRAPH:

Claims 68 and 70-73 have been rejected as lacking enabling disclosure in the specification. Applicants disagree but have cancelled the rejected claims in an effort to expedite prosecution. Applicants fully intend to pursue the method claims in a later continuing application.

THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION:

The Examiner has raised two double patenting rejections against the pending claims. The first is over claims 1-6 of U.S. Patent No. 5,866,702. Applicants are confused however as only one of the claims rejected by the Examiner is still pending. Claims 1, 2, 8, 10, 14-16, 18, 20, and 44-47 were cancelled in the preliminary amendment filed with the application. As claim 48 is still pending, applicants are submitting a Terminal Disclaimer with the present communication, disclaiming the terminal portion of any patent issuing on the present continuing application that would extend beyond the term of U.S. Patent No. 5,866,702. Submission of this Terminal Disclaimer is not intended as acquiescence in the double patenting rejection, but is solely for the purpose of expediting prosecution.

The Examiner provisionally rejected claims 48-50, 53-62, and 65-67 under the judicially created doctrine of obviousness-type double patenting over claims 92 et al. of copending U. S. Patent Application Serial No.09/929,772. As with the rejection over U.S. Patent No. 5,866,702, applicants are submitting a Terminal Disclaimer with the present communication, disclaiming the terminal portion of any patent issuing on the present continuing application that would extend beyond the term of any patent that might issue from U. S. Patent Application Serial No.09/929,772. Submission of this Terminal Disclaimer is not intended as acquiescence in the double patenting rejection, but is solely for the purpose of expediting prosecution.

CONCLUSION

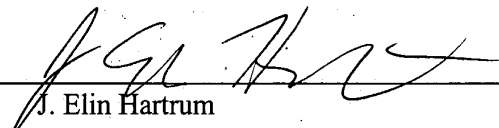
For the foregoing reasons, applicant submits that the claims comply with the requirements of 35. U.S.C. §§112, 102(b), and 103(a) and are in condition for allowance. A Notice of Allowance is requested, and a prompt mailing thereof would be much appreciated.

Should the Examiner have any questions regarding this amendment, he or she is welcomed to contact the undersigned attorney at (650) 384-8755. Applicants respectfully request that all further communication be sent to the undersigned attorney at the following address:

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Respectfully submitted,

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